Remarks/Arguments

Claims 8-11 and 14-16 are pending in the application. Reconsideration and allowance is requested in view of the above changes and the following remarks.

35 USC § 112 – Written Description

Claims 8-11 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically, Examiner states that the claims contain subject matter which was not described in the specification in such a way as to convey to the skilled person that the inventor was in possession of the claimed invention.

Applicant disagrees with Examiner's assertions.

Examiner states on the last line of page 3 of the office action of September 7, 2010 (hereinafter "the office action"), that "*Applicants have not described the genus of claimed complexes such that the specification might reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed*".

Applicant submits that the written description provisions have been both met and exceeded. In particular, Examiner's attention is drawn to the examples set out on pages 12 to 18 of the instant specification. These examples exemplify the invention for mammalian cells infected with the bacteria *M. bovis* (example 1), mammalian cells (rat liver hepatocytes) infected with the parasite Plasmodium Berghei (Example 2) and mammalian cells (mouse peritoneal macrophages) infected with the bacteria *M. tuberculosis* as disclosed in Example 4. Hence, in as far as, for example, bacterial intracellular pathogens are concerned, more than one example has been provided.

Furthermore, at page 4 of the office action, Examiner states that "The nucleic acid itself is required". Applicant strongly contends that this is not relevant to the written description of the instantly claimed invention. As previously argued by Applicant, the present invention provides a crude composition comprising stress protein / peptide complexes which are *not* purified to homogeneity (see page 13, lines 21-24 of the instant specification). There is no requirement for the specific composition of these complexes to be known, neither at the amino acid level and certainly not at the nucleic acid level.

In fact, and as previously stated, to analyze the stress protein complexes at the amino acid or nucleic acid level would be completely contra-intuitive to the instant invention, where the simplicity and ingenuity of the invention relates to the ability to use the obtained, non-homogenous complexes to confer broad immunogenicity in a subject to whom the complexes are administered.

Examiner continues at page 5, line 3 of the office action that "*...factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification*". Applicant strongly disagrees with this statement. Applicant again refers Examiner to the Examples set out in the instant specification. These examples clearly show how the complexes of the instant invention can be made (Examples 1 and 2) and, in turn, how they can be used to immunize a subject to confer protective immunity against a pathogen.

Examiner's citation of Greenspan and Chothia and their inclusion as support to the written description rejection are wholly irrelevant. There is no need to define epitopes, just as there is no need to disclose nucleic acid sequences.

Applicant refers to US Patent No. 5,961,979 ("Srivastava") which has been cited by Examiner in the office action. This *granted* US Patent contains claims which are directed to compositions comprising stress protein / peptide complexes. Yet, there is no disclosure in that patent of nucleic acid sequences. Srivastava does disclose a limited number of amino acid sequences, but that is for the purpose of allowing the production of a *recombinant* stress protein complex. The instantly claimed invention does not extend to recombinantly produced stress protein complexes. Rather, the complexes are produced within the infected cell, using stress proteins derived from the host cell, or from the infecting pathogen.

Furthermore, at page 7 of the office action, Examiner states that "*...written support cannot be found for any stress proteins that are produced by intracellular pathogens*". Examiner contends that the description does not provide any written support for stress proteins being derived from the intracellular pathogen itself; rather that it only describes the pathogen inducing the host cell to produce stress proteins of its own.

Examiner continues by referring to the specification at pages 5 and 6 and also at 9 and 10. However, Examiner appears to misinterpret these sections. For example, page 6, lines 20-23

state that "*The terms stress proteins and heat shock protein, as used herein, include those proteins that comprise the GroEL, GroES and DnaK and DnaJ families of bacterial HSPs*".

The examples show that *mammalian cells* are infected with intra-cellular pathogens. Hence, for the eventual stress protein complexes to contain stress proteins which comprise GroEL, GroES, DnaK and DnaJ, this makes it clear that some of the stress proteins of the stress protein / antigenic peptide fragment complexes are derived from the intracellular pathogen (because GroEL, GroES, DnaK and DnaJ stress proteins are *all* bacterial stress proteins). If the stress proteins were limited to HSP70 etc., then these could be mammalian cell stress proteins.

Furthermore, the instant specification states at page 6, lines 28 to 30 that "*Preferably the vaccine contains a plurality of SP/antigenic peptide fragment complexes derived from the stressed pathogen. We particularly prefer that the GroEL, GroES, DnaK and DnaJ families of proteins are used as immunogenic determinants in the present invention, with DnaJ and GroEL ((i.e. bacterial stress proteins)) most preferred*".

This teaching therefore makes is absolutely clear that the stress proteins of the invention may be derived from an intra-cellular pathogen. Hence, it is unfairly limiting of Examiner to construe the instant specification to be limited to stress proteins derived from the infected mammalian cells only.

Furthermore, the skilled person, when reviewing the examples of the instant specification would observe that the methods disclosed for the production of the stress proteins would result in the membranes of *both* the mammalian cell and the infecting intracellular pathogen being solubilized. This is evident in the description of the instant specification at page 12, line 31 through to page 13, line 24. An excerpt of this reads "*...after which the cells are then disrupted using a cell homogeniser..... Alternatively, the homogenisation buffer may contain detergent, such as PBS with 0.5% Tween, the detergent composition being ... suitable to solubilise the cell membrane.*

In conclusion, Applicant submits that specific support does exist within instant specification for the claims to extend to the inclusion of stress proteins derived from the intracellular pathogen.

35 USC § 112

Response to Section 102 Rejection over Srivastava (WO 95/24923)

Claims 8-11 and 14-16 have been rejected as allegedly anticipated by Srivastava WO 95/24923. Applicant respectfully submits that the claims of the instant application are not anticipated by the teaching of Srivastava.

Examiner has considered the arguments previously submitted by Applicant and has addressed these.

On page 13 of the office action, Examiner states that "*Applicants argue that Srivastava describe stress peptide complexes purified to homogeneity. They argue that, accordingly, these complexes can comprise only a single stress protein species. ... These arguments are not commensurate in scope with the claimed invention. The claims do not require the use of more than one stress peptide. In fact the claims recite the complex is between a stress induced protein* [not plural] *and an antigenic determinant*".

Applicant disagrees with this analysis of Examiner in coming to this conclusion. Examiner has isolated only part of the claimed integer and therefore interpreted the stress induced protein feature out of context. In particular, the full integer of the claim reads; "*...wherein the immunogenic determinant comprises a mixture of complexes between a stress induced protein and an antigenic peptide fragment*". Hence, the key term is "*a mixture of complexes*" as this feature precedes the stress protein feature and therefore requires that the complexes are *different*, thus providing the required *mixture*. A plurality of complexes which are the same *cannot* constitute a mixture.

Examiner further submits that there is not a structural difference between the complexes of the present invention and those of Srivastava. This is an incorrect assumption. The complexes of Srivastava relate only to stress proteins comprising a single class of mammalian stress protein. Conversely, the complexes of the instantly claimed invention contain different types of mammalian stress protein and *also* stress proteins derived from the invading pathogen.

For example, page 27, line 11 onwards of Srivastava relates to complexes where the stress protein is HSP70; page 29, line 7 onwards relates to the stress protein being HSP90; and page 30, line 7 onwards relates to the stress protein being gp96. As previously pointed out, the

discussion of bacterial stress proteins at Srivastava page 23 is merely background information relating to what a heat shock protein is. Srivastava does not state that non-mammalian stress proteins can be used.

These examples support the fact that Srivastava relates to the isolation of a stress protein of a single class. The complexes of Srivastava are *not* mixtures comprising different stress proteins, as is required by the claims of the instant invention and they are *not* mixtures of stress proteins derived from the host cell and the invading intracellular pathogen.

To further support this and to reinforce the fact that Examiner is conferring on Srivastava a broader interpretation of what is actually disclosed, Applicant refers to page 27 of Srivastava which disclose the purification of stress protein complexes. The conditions set out (i.e. use of a mechanical shearing) would not result in the disruption of the cell walls of an intracellular pathogen contained within a mammalian cell. Accordingly, the subsequent complexes will only comprise mammalian heat shock proteins. This is in stark contrast to the method of the instant invention, where the cell wall of both the infected mammalian cell and the intracellular pathogen are disrupted, thus making stress proteins from both the mammalian host cell and the intracellular pathogen available for inclusion in the complex mixture.

Applicant therefore respectfully submits that, contrary to Examiner's assertions, there is a structural difference between the product claimed and the product taught by the prior art. Claims 8-11 and 14-16 do not lack novelty over Srivastava (WO 95/24923).

Response to Section 102 Rejection over Srivastava (US 5,961,979)

Claims 8-11 and 14-16 have been rejected as allegedly anticipated by Srivastava US 5,961,979 ("Srivastava US '979").

Applicant previously also submitted the distinction between the T-cell immune response mediated by Srivastava and the combined cytotoxic T cell response and B cell humoral (antibody mediated) response conferred by the instant invention and as exemplified in the examples.

Applicant disagrees with Examiner's assertion on page 14 that "*Srivastava teaches that a strong T-cell immune response was raised does not negate or teach away from there also being*

an antibody immune response present. Since Srivastava teaches structurally analogous structures, they would inherently price the same types of immune response".

Applicant submits that this is mere conjecture on the part of Examiner. Furthermore, there would be no motivation for the skilled person to seek an immune response which mediated both a cell mediated and humoral response. The skilled person would be well aware that when administering an immunogenic composition to a subject, typically either a cell mediated or humoral response would be desired, this being dependent upon the pathogen which was being targeted.

Srivastava US '979 is littered with statements intimating that a cytotoxic T cell (cell mediated) response would result from administration of the compound of Srivastava. For example column 4, line 55 states that "It has now been discovered that a subunit vaccine containing a stress protein peptide complex when isolated from cells infected with a pre-selected pathogen intracellular pathogen and then administered to a mammal can effectively stimulate cellular immune responses against cells infected with the same pathogen. Specifically, the immune response is mediated through the cytotoxic T cell cascade". Similarly, at page 9, lines 21-22 of his WO95/24923 (discussed above), Srivastava states that the preferred embodiment of both inventions comprises "a vaccine that can be administered to a mammal for inducing in the mammal a cytotoxic T cell response", and that "The vaccines manufactured in accordance with the principles described herein *contain an immunogenic stress protein-peptide complex that is capable of stimulating in the recipient a cytotoxic T cell response*" at page 9, lines 25-29.

In targeting an intracellular pathogen, it is recognized that cell mediated immunity would be the route of choice to eradicate such pathogens. Hence, there would be no motivation to Srivastava to produce both a cell mediated and humoral response. Furthermore, as the complexes of Srivastava do not contain intracellular pathogen derived stress proteins, any humoral response would be less effective than the humoral response mediated by and exemplified by the instant invention.

Furthermore, there is no teaching or suggestion in Srivastava US '979 that *mixtures* of stress protein / peptide complexes can be used as the immunogenic determinant in a vaccine composition. Rather, Srivastava US '979 is continually focused on purifying or isolating

complexes to provide homologous preparations. Because of the inclusion of the word "can" in this statement at column 14, line 30 that *"The Hsp-70 peptide complex can be purified to apparent homogeneity using this method"* Examiner states that complexes the same as those of the instantly claimed invention can be obtained by Srivastava US '979. Examiner is incorrect. Nowhere in Srivastava US '979 is the administration of a composition comprising a mixture of stress protein / peptide complexes disclosed. In fact, Srivastava US '979 is more focused on the production of recombinant complexes which have a known structure.

Furthermore, Srivastava US '979 is only concerned with complexes where the stress protein is a mammalian complex. For example, columns 13 and 14 relate to complexes where the stress protein is HSP70; column 14, line 47 onwards relates to the stress protein being HSP90; and the bottom of column 15, line 12 onwards relates to the stress protein being gp96. As previously pointed out, the discussion of bacterial stress proteins at column 11 is merely background information relating to what a heat shock protein is. Srivastava US '979 does not state that non-mammalian stress proteins can be used and nowhere in the description does Srivastava US '979 discuss purifying complexes comprising stress proteins from intracellular pathogens.

These examples support the fact that Srivastava US '979 relates to the isolation of a stress protein of a single class. The complexes of Srivastava US '979 are *not* mixtures comprising different stress proteins, as is required by the claims of the instant invention and they are *not* mixtures of stress proteins derived from the host cell and the invading intracellular pathogen.

To further support this and to reinforce the fact that Examiner is conferring on Srivastava US '979 a broader interpretation than what is actually disclosed; Applicant refers to column 13, lines 54 to 66 which disclose the purification of stress protein complexes. The conditions set out (i.e. use of a dounce homogenizer) would not result in the disruption of the cell walls of an intracellular pathogen contained within a mammalian cell. Accordingly, the subsequent complexes will only comprise mammalian heat shock proteins. This is in stark contrast to the method of the instant invention, where the cell wall of both the infected mammalian cell and the intracellular pathogen are disrupted, thus making stress proteins from both the mammalian host cell and the intracellular pathogen available for inclusion in the complex mixture.

Applicant therefore respectfully submits that, contrary to Examiner's assertions, there is a structural difference between the product claimed and the product taught by the prior art. Claims 8-11 and 14-16 do not lack novelty over Srivastava US '979.

Status of Application No. 10/363,454

The status of the '454 application, since the last action reported (an office action mailed February 19, 2010) is as follows. A response to the February 19, 2010 office action was filed. A further office action was issued on February 3, 2011. Applicant has not yet filed a response to the February 3, 2011 office action.

A copy of the February 3, 2011 office action is submitted herewith.

Status of Application No. 10/049,704

The status of the '704 application, since the last action reported (an office action mailed Sept. 18, 2009) is as follows. A response to the office action was filed March 18, 2010. A further office action was mailed August 17, 2010, to which applicant responded on February 17, 2011.

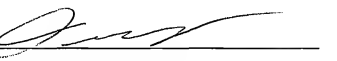
A copy of the August 17, 2010 office action is submitted herewith, along with copies of non-US patent Examiner-cited references.

Conclusion

The claims remaining in the application are believed to be in order for allowance. An early action toward that end is earnest solicited.

Respectfully submitted

CAMILO ANTHONY LEO SELWYN COLACO

BY 

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